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| 10/688,198 | 10/17/2003 | Gerardo Zapata | ABGENIX.057A | 6664 |

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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

| EXAMINER | |
|---|---|
| BRISTOL, LYNN ANNE | |
| ART UNIT | PAPER NUMBER |
| 1643 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | NOTIFICATION DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 12/21/2006 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 12/21/2006.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/688,198 | ZAPATA, GERARDO | |
| | Examiner | Art Unit | |
| | Lynn Bristol | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. The Examiner gratefully acknowledges Applicants participation in the interview of September 27, 2006.

2. Claims 1 and 7 have been amended and Claims 26-29 cancelled by amendment in the Response of 10/16/06.

3. Applicants have not identified support for the amended claims in the original specification, but which can be found on p. 13, [0041], for example.

4. Claims 1-25 are all the pending claims for this application.

### *Species Restriction Maintained*

5. Applicants comments on p. 7, ¶ 3 of the Response of 10/17/06 have been considered regarding the rejoinder of non-elected species for antibody-cleaving enzymes of Claims 8 and 9.

6. Applicants comments on p. 8, ¶3 of the Response of 10/17/06 have been considered regarding the rejoinder of non-elected species for cell lines of Claim 11.

### ***Objections Withdrawn***

### *Specification*

7. The objection to the abstract and page 2 of the specification for including the attorney docket no. is withdrawn in view of Applicant' comments during the interview of September 27, 2006 and on p. 7, ¶4- p. 8, ¶1 in the Response of 10/16/06.

8. The amendment of the specification to properly recite the trademark for XenoMouse™ has been entered and the objection withdrawn. Applicants on p. 8, ¶2 of the Response of 10/16/06 are acknowledged.

## ***Rejections Withdrawn***

### *35 USC § 112- first paragraph-enablement*

9. The rejection of Claims 1, 3-7 and 10-18 under 35 U.S.C. 112, first paragraph, in lacking enablement for making and using any antibody fragments that do not retain binding activity or which cannot be used in immunoassays, immunotherapeutics or immunodiagnostics, is withdrawn in view of the amendment of Claim 1 to recite "antigen-binding fragments of an antibody" and Applicant's comments on p. 9, ¶3 in the Response of 10/16/06.

### *35 USC § 103*

10. The rejection of Claims 1-7, 10, 11, 13 and 16-18 under 35 U.S.C. 103(a) as being unpatentable over Takai and Parham is withdrawn. Applicant's arguments filed on p. 10, ¶1-5 of the Response of 10/16/06 have been fully considered and are persuasive.

The Examiner submits that neither Takai nor Parham alone or in combination disclose adjusting the culture medium to activate an endogenous enzyme.

11. The rejection of Claims 1, 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Takai, Parham, Zhang, and Schifferli is withdrawn. Applicant's

arguments filed on p. 10, ¶6 of the Response of 10/16/06 have been fully considered and are persuasive.

See the Examiner's comments supra with respect to the Takai and Parham references.

12. The rejection of Claims 19, 21, 24 and 25 under 35 U.S.C. 103(a) as being unpatentable over Takai and Parham is withdrawn. Applicant's arguments filed on p. 11, ¶1 of the Response of 10/16/06 have been fully considered and are persuasive.

See the Examiner's comments supra with respect to the Takai and Parham references.

13. The rejection of Claims 19 and 20 under 35 U.S.C. 103(a) as being unpatentable over Takai, Parham and Schifferli is withdrawn. Applicant's arguments filed on p. 11, ¶2 of the Response of 10/16/06 have been fully considered but are persuasive.

See the Examiner's comments supra with respect to the Takai and Parham references.

14. The rejection of Claims 19, 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over Takai, Parham and Mason is withdrawn. Applicant's arguments filed on p. 11, ¶3 of the Response of 10/16/06 have been fully considered and are persuasive.

See the Examiner's comments supra with respect to the Takai and Parham references.

***Rejections Maintained***

***35 USC § 112- second paragraph***

15. The rejection of Claim 1 (and dependent claims 2, 6-15) under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation "adjusting the conditions of the cell media" is maintained.

Applicant's arguments filed on p. 8, ¶4- p. 9, ¶1 in the Response of 10/16/06 have been fully considered but they are not persuasive. Applicants allege "...the limitation requires that conditions be adjusted in the cell media (in which the cell line is growing), and that at least one endogenous enzyme (already in the cell media) be activated as a result of "adjusting the conditions." Accordingly, such "adjusting" is not met by merely adding a new enzyme to the cell media" (p. 9, ¶1).

In response to applicant's argument, it is noted that the features upon which applicant relies are not recited in the rejected claim(s). The "adjusting" step does not preclude adding a new enzyme or any supplement to the medium to activate for example, a preproenzyme. The "adjusting" step encompasses any manipulation to the cell medium.

For all of these reasons the rejection is maintained.

***35 USC § 112- first paragraph-biological deposit requirement***

16. The rejection of Claim 12 under 35 U.S.C. § 112, first paragraph, as being drawn to the cell line CHO-DG44 and requiring a biological deposit is maintained. Applicants comments on p. 9, ¶2 of the Response of 10/16/06 and the copies of the commercial

data sheets from Irvine and Xcellerex and the printout of references from a PubMed search of the CHO-DG44 cell line are not sufficient in establishing that the CHO-DG44 cell line is commercially available.

In the Office Action of 6/22/06, Applicants were requested to verify whether the ATCC deposit of the CRL-9096 clone for a dhfr deficient CHO cell line was the same as the claimed CHO-DG44 cell line in order to ensure that a cell line is commercially or publicly available. Applicants have instead provided three reference sources, which they allege to be examples of a commercially available cell line. The Irvine Scientific data sheet for IS CHO culture medium shows CHO DG44 cell growth in Figure 1, but the Examiner's search of the website indicates that Irvine Scientific does not sell the CHO DG44 cell line (see copy of search output). The Xcellerex data sheet for PDMax or Supercell discloses a CHO DG44 cell line, but the Examiner search of the Xcellerex website reveals that the CHO DG44 cell line comprises a genome-integrated vector for gene targeting transfection, and it is unclear if this is the same claimed cell line and disclosed in the original specification [0048]. Finally, the Examiner acknowledges the PubMed search output for publication literature on CHO-DG44 cells but again Applicants have not met the burden of establishing public availability for the instant claimed cell line, i.e., meeting the terms and conditions of the Budapest Treaty.

## ***New Grounds for Rejection***

### *Claim Rejections - 35 USC § 112*

17. Claims 1-20 and 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-18 are indefinite for the recitation "endogenous enzyme" because in Claim 1 it is unclear where an "endogenous enzyme" is located for targeted activation. A copy of a dictionary definition (Merriam-Webster) for the term "endogenous" states: "produced or synthesized within the organism or system", thus an endogenous enzyme may be present in or produced by the cultured host cell itself and this limitation is not set forth in the claims. It is noted that Claim 1 does not recite a step for specifically removing the cultured cells from the cell medium, thus it is not clear if "endogenous" refers to enzymes in cell medium or associated with the cells.

The specification teaches and as Applicants state on p. 9, ¶1, "at least one endogenous enzyme (already in the cell media) be activated". Further Claim 19 recites that the enzyme is "in said cell media". Thus claims 1-18 encompass any medium-associated or extracellular and intracellular endogenous enzymes.

b) Claims 19, 20 and 22-25 are indefinite for the recitation "activating endogenous aspartyl enzyme activity" because in Claim 19 it is unclear what is meant by "activating". The claims broadly encompass any manipulation to the cell medium in order to activate aspartyl enzyme.

***Claim Rejections - 35 USC § 112, first paragraph: enablement***

18. Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating antibody fragments according to the method steps of clarifying the conditioned media, stabilizing the temperature at 37°C, and adjusting the pH to about 3.5 to activate endogenous enzymes for cleaving Ig molecules, does not reasonably provide enablement for any adjustment to the cell media to activate an endogenous enzyme to specifically cleave an antibody in order to generate antibody binding fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The interpretation of Claims 1-25 is of record and discussed supra.

The specification discloses the method steps for activating an endogenous enzyme (i.e., aspartyl and cysteinyl proteases) in the culture medium in order to proteolytically cleave an IgG antibody having been secreted from a host cell. Notably, the enzyme is not endogenous to the cell itself, but endogenous to the culture medium. The method requires removing the cells from the medium in which they are growing in order to practice the activation step. The specification discloses adjusting the clarified culture medium to 37°C, stabilizing the temperature, followed by adjusting the pH of the cell culture fluid with 5N NaOH and 6N HCl. The specification discloses that maximal activity of endogenous enzymes in the cell culture medium of a cell culture expressing IgG occurred at pH of 3.5 [0050-0051].

The Examiner understands that the performance of these method steps is required in order to obtain an intact, antigen-binding fragment of an antibody. Otherwise it is not understood how given the breadth of the instant method claim scope, the resultant effect would be a total and non-specific degradation of the antibody.

***Conclusion***

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER